CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-024/S-005

CORRESPONDENCE

Aventis Pharmaceuticals

Aventis

June 28, 2000

NEW CORRESPONDENCE

Food and Drug Administration
Division of Special Pathogen and Immunologic
Drug Products, HFD-590
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Corporate Building
9201 Corporate Blvd.
Rockville, MD 20850

Subject: **PRIFTIN® (rifapentine) 150 mg Tablets**
Approved NDA 21-024
General Correspondence: SE-007

SNC-005

Dear Madam/Messieurs:

In reference to an efficacy supplement submitted on April 13, 2000 and to a conversation with Diana Willard on May 15, 2000, Diana requested a debarment certification, financial disclosure, and patent information/certification for the above-mentioned efficacy supplement. This efficacy supplement provides labeling revisions based on the Final Clinical Study Report of Protocol 008.

Attached is the debarment certification and patent information/certification, which was submitted in Volume 1.1 of the original NDA on December 22, 1997. Regarding the request for financial disclosure, Protocol 008 was conducted prior to the final rule on financial disclosure, therefore, it was not collected for Protocol 008 and is not included for this supplement.

Please contact me at 816-966-5381 (FAX: 816-966-6794) if you have any questions regarding this correspondence.

Sincerely,

Carol A. Childers

Carol Childers, PharmD
US Regulatory Affairs, Marketed Products
Aventis Pharmaceuticals Inc.

ORIGINAL

Enclosures: Patent Information/Certification
Debarment Certification

Hoechst Marion Roussel

June 22, 1998

M. Dianne Murphy, MD
Office of Drug Evaluation IV
Center for Drug Evaluation and Research Food and Drug Administration
9201 Corporate Blvd., 4th Floor
Rockville, MD 20857

Hoechst Marion Roussel, Inc.
10236 Marion Park Drive
Mail: P.O. Box 9627
Kansas City, MO 64134-0627
Telephone (816) 966-5000

BY FAX: 301-827-2520

Subject: **NDA 50-752**
PRIFTIN®
(rifapentine)
Label revision incorporating labeling statement related to Accelerated Approval

Dear Dr. Murphy:

Hoechst Marion Roussel has reviewed and evaluated the labeling statement related to Accelerated Approval provided this midday, June 22, 1998. Our decision is to accept your proposed language and to further accept option 2, the addition of the labeling statements provided to the "Indications and Usage" section and the "Clinical Trials" section of the labeling.

A copy of the PRIFTIN label designated "clean008", is attached to this letter. The requested changes are on pages 6 and 9.

Please contact me if you have any questions regarding this submission.

Sincerely,

Libby Hayes

Libby Hayes, Manager
U.S. Drug Regulatory Affairs

DIV

NDA 21-024

JUN 22 1998

Hoechst Marion Roussel, Inc.
Attention: Ms. Libby Hayes, B.S.
10236 Marion Park Drive
P.O. Box 9627
Kansas City, MO 64134-0627

Dear Ms. Hayes:

Please refer to your new drug application dated December 22, 1997, received December 22, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PRIFTIN® (rifapentine) 150 mg tablets.

We acknowledge receipt of your submissions dated as follows.

January 23, 1998	March 19, 1998	June 3, 1998
January 28, 1998	March 27, 1998	June 4, 1998
January 29, 1998	April 6, 1998	June 5, 1998
February 3, 1998	April 13, 1998	June 9, 1998
February 5, 1998	April 28, 1998	June 10, 1998
February 9, 1998	April 30, 1998	June 11, 1998
February 16, 1998	May 12, 1998	June 16, 1998
March 3, 1998	May 19, 1998	June 22, 1998
March 16, 1998	May 22, 1998(3)	
March 18, 1998	May 29, 1998	

The User Fee goal date for this application is June 22, 1998.

This new drug application provides for the use of PRIFTIN® (rifapentine) 150 mg tablets in the treatment of pulmonary tuberculosis.

We have completed the review of this application, including the submitted draft labeling, according to the regulations for accelerated approval and have concluded that adequate information has been presented to approve PRIFTIN® (rifapentine) 150 mg tablets for use as recommended in the draft labeling in the submission dated June 15, 1998, as revised on June 22, 1998. Accordingly, the application is approved under 21 CFR 314.510. Approval is effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on June 22, 1998. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 21-024. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of labeling may be required.

Products approved under the Accelerated Approval Regulations (21 CFR 314.510) require further adequate and well-controlled studies to verify and describe clinical benefit. The accelerated approval commitments are not specifically designated in your June 15, 1998, letter; therefore, they are listed as follows:

1. The final Clinical Study Report issued upon completion of Clinical Study 008 will be submitted to the Agency for review. The projected timing is June 1999. In this final report both safety and efficacy data for the 2 years of followup will be included.

2. You will continue to provide support for USPHS 22, conducted under the Center for Disease Control's (CDC) Investigational New Drug (IND) application for rifapentine, and to provide support for the pharmacokinetic sub-study undertaken in Study 22, developed because of the occurrence of rifampin monoresistance in four HIV-infected patients who relapsed in the rifapentine treatment arm. It is agreed, since this study is being conducted by CDC under a separate IND, CDC will submit study results upon completion of the study.

We remind you of your Phase 4 commitments specified in your submission dated June 15, 1998, and to our June 11, 1998, facsimile, and to our letter dated June 5, 1998. These commitments, along with any completion dates agreed upon, are listed below.

1. You commit to continue collaborations with CDC on further characterizing the activity of PRIFTIN® against pulmonary tuberculosis.

2. You should submit study reports on the mouse and rat carcinogenicity studies when they have been completed. The projected timing is April-May 2000.

3. You commit to revising the analytical method for [redacted] in rifapentine tablets and submitting the method and validation report to the FDA. In addition, any revised specification for the [redacted] impurity and total impurities in the tablets will be supported by available data and communicated to the FDA.

4. You commit to evaluate the pharmacokinetics of rifapentine and its major metabolite in children under 12 years of age. The currently available 150 mg film-coated tablet may not be suitable for administration to very small children.

The following microbiology studies are also part of your phase 4 commitments:

- Additional studies to adequately determine the rifapentine breakpoints for *M. tuberculosis* (MTB) strains are needed. Effects of test conditions on rifapentine MICs should be determined using both the radiometric method (should you choose to pursue this methodology) and the agar proportion method. This is necessary as approximately 25 percent of the clinical laboratories in the United States still perform mycobacterial susceptibility testing using the agar proportion method.

- The comparison of rifapentine MICs to rifampin MIC values is necessary to further characterize the cross resistance pattern observed in the clinical trial. For the evaluation of susceptibility both rifampin and rifapentine should be tested in serial 2 fold dilutions. The MTB strains used in the susceptibility studies should include both rifampin susceptible and resistant clinical isolates and established QC strains. The design of each study and the number of MTB isolates to be tested should be discussed with the Division's microbiologist prior to performing the susceptibility tests.

    1. Studies should be conducted to test the effects of the following on rifapentine MIC values:
        a. different lots and sources of media (test a minimum of three different lots from two manufacturers)
        b. commercial media versus media made in the laboratory
        c. age of the media (new versus lots near the expiration date)
        d. the addition of nutrients in the medium (e.g 10 percent OADC and middlebrook 7H11 versus 7H10)
        e. various concentrations of [redacted]

    2. The following tests need only be conducted if alterations are made to any of the conditions currently established for the agar proportion or the radiometric broth susceptibility testing methods:
        a. pH of the medium

b. log phase growth of MTB isolates used for inoculation of susceptibility test medium
c. inoculum size of MTB isolates

3. Studies should be conducted to determine how long rifapentine containing susceptibility media (agar plates and 7H12 broth containing rifapentine) can be held prior to conducting susceptibility testing. This is necessary to ensure that drug stability in the medium is not a source of variability in the determination of rifapentine MICs.

4. ATCC control strains 27294 and 35838 are recommended by the NCCLS as control strains for rifampin testing. Please provide the rationale for the use of a different rifamycin resistant strain in your susceptibility studies. It is highly recommended that ATCC strains 27294 and 35838 be used when performing any susceptibility testing. This is encouraged as many of the medical laboratories in the U.S. already have and use these QC strains on a regular basis.

5. Currently, a population of 1 percent resistant MTB organisms is considered clinically significant. A minimum detection level of 10 percent resistance (as defined for the radiometric broth method) is unacceptable. If you choose to pursue this method then additional studies should be conducted to further characterize what percentage of rifampin and rifapentine resistant isolates are not detected using the NCCLS radiometric broth method. Alterations to the methodology should be investigated to reduce the limit of detection of resistance to 1 percent for both rifampin and rifapentine.

6. After the susceptibility testing methods have been characterized and standardized, a new study should be conducted to determine the inter- and intra- laboratory variation of rifapentine MICs. In this study at least 100 clinical isolates with varying rifapentine MICs as well as the proposed QC strains should be sent to at least 3 reference laboratory sites. At each site, rifapentine MICs should be measured using the proposed agar proportion and radiometric broth susceptibility testing methods. QC strains should be included with each susceptibility test run and MICs determined against both rifampin and rifapentine. Rifapentine should be tested in a range of concentrations to facilitate in the determination of the final breakpoints.

7. Please provide a detailed explanation as to the type of studies that will be conducted in phase B of your program to validate susceptibility testing methods.

8. After the susceptibility tests are completed the test results along with the raw data should be submitted to the Division for review. At the same time please submit your proposal for the marketing of suitable rifapentine preparations at the proposed concentrations for the determination of rifapentine resistance in M. tuberculosis strains. After the rifapentine breakpoints have been established for both the agar proportion method and the radiometric broth method, adequate stability studies must be performed to determine the expiration dates for the commercial products containing the designated rifapentine concentrations.

In the design of any future rifapentine pharmacokinetic studies you agreed to consider the following.

- If an indication in HIV positive patients is further explored you would consider conducting additional pharmacokinetic drug-drug interaction studies with drugs metabolized by CYP 3A, especially other protease inhibitors and fluconazole.

- Evaluate the efficacy of rifapentine using higher dosing frequency in order to determine the optimum dosing regimen for this drug. Pharmacokinetic modeling techniques can be used to predict what might be the optimum dosing regimen from the current pharmacokinetic data when rifapentine was given 3 times a week and daily.

We also remind you that validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. Should an IND not be required to meet your Phase 4 commitments, please submit protocol, data, and final reports to this NDA as correspondences. In addition, we request under 21 CFR 314.81(b)(2)(vii) that you include in your annual report to this application, a status summary of each commitment. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

We also remind you that, under 21 CFR 314.550, after the initial 120 day period following this approval, you must submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Brenda Atkins, Project Manager, at (301) 827-2127.

Sincerely yours,

/S/

M. Dianne Murphy, M.D.
Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

DIV. FILE
NDA 21-024

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

APR 25 2000

NDA 21-024/S-005

PRIOR APPROVAL SUPPLEMENT

Aventis Pharmaceuticals, Inc.
Attention: Carol Childers, Pharm.D.
US Regulatory Affairs, Marketed Products
10236 Marion Park Drive
P.O. Box 9627
Kansas City, Missouri 64134-0627

Dear Dr. Childers:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Priftin® (rifapentine) Tablets, 150 mg

NDA Number: 21-024

Supplement number: S-005

Review Priority Classification: Standard (S)

Date of supplement: December 17, 2000

Date of receipt: December 21, 2000

This supplemental application proposes the following change:

> Revisions to the Clinical Trials, Indications and Usage, and Adverse Reactions sections of the labeling based upon the Final Clinical Study Report for Protocol 008, "Efficacy and Safety of Rifapentine Combination Therapy Compared to Standard Therapy in the Treatment of Previously Untreated Pulmonary Tuberculosis."

This application was filed under section 505(b) of the Act on February 19, 2000 in accordance with 21 CFR 314.101(a).

The primary user fee goal date will be October 21, 2000 and the secondary user fee goal date will be December 21, 2000.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:

Center for Drug Evaluation
and Research
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Attention: Document Control Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation
and Research
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Attention: Document Room
9201 Corporate Boulevard
Rockville, Maryland 20850

If you have any questions, call Diana Willard, Regulatory Project Manager, at (301) 827-2127.

Sincerely,

/S/

Ellen C. Frank, R.Ph.
Chief, Project Management Staff
Division of Special Pathogen and
Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research